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09/214,453	10/25/1999	PETER FRANCIS LEADLAY		8705

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ART UNIT	PAPER NUMBER
1652	26

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/214,453	LEADLAY ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,25-27,31-37,39,44 and 47-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,25-27,31-37,39,44 and 47-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Application Status

1. In response to the previous Office action, a final rejection (Paper No. 19, mailed on May 21, 2002), Applicants filed numerous amendments and responses received on November 25, 2002 (Paper No. 21), on February 21, 2003 (Paper No. 23), on April 24, 2003 (Paper No. 24), and on June 13, 2003 (Paper No. 25). All tolled Claims 3, 24, 45, and 46 have been cancelled, Claims 25, 26, 31, 33-37, 39, 44, 47, and 50-56 have been amended and Claims 59-68 have been added. Thus, Claims 1, 2, 25-27, 31-37, 39, 44, and 47-68 are pending in the instant Office action and will be examined herein.

Priority

2. As previously noted, the instant application is granted the benefit of priority for the International Application No. PCT/GB97/01819 filed on July 4, 1997 which claims benefit of (1) U.S. Provisional Application No. 60/024,188 filed on August 19, 1996, (2) Great Britain foreign application 9614189.0 filed on July 5, 1996, and (3) Great Britain foreign application 971062.3 filed on May 28, 1997.

Drawings

3. As previously noted, the drawings are considered informal for the reasons detailed in the PTO Form 948 attached to the previous Office action (Paper No. 16). Appropriate correction is required in response to the instant Office action and **may not** be held in abeyance (see 37 C.F.R. § 1.85(a)).

Withdrawn - Objections to the Specification

4. Previous objection to the typographical error in the amendment filed March 21, 2002, to page 63, line 7, is withdrawn by virtue of Applicants' amendment.

5. Previous objection to the amendment filed March 21, 2002 (Paper No. 17) under 35 U.S.C. § 132 for introducing new matter into Claims 45, 46,and 52 is withdrawn by virtue of Applicants' cancellation and/or amendment of the new matter.

Withdrawn - Claim Rejections - 35 U.S.C. § 112

6. Previous rejection of Claim 24 under 35 U.S.C. § 112, second paragraph, is withdrawn by virtue of Applicants' cancellation of said claim.

7. Previous rejection of Claim 45 under 35 U.S.C. § 112, second paragraph, is withdrawn by virtue of Applicants' cancellation of said claim.

8. Previous rejection of Claim 46 under 35 U.S.C. § 112, second paragraph, is withdrawn by virtue of Applicants' cancellation of said claim.

9. Previous rejection of Claim 29 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of Applicants' cancellation of said claim.

10. Previous rejection of Claim 29 under 35 U.S.C. § 112, first paragraph, scope of enablement, is withdrawn by virtue of Applicants' cancellation of said claim.

11. Previous rejection of Claim 39 under 35 U.S.C. § 112, first paragraph, scope of enablement, is withdrawn here but reiterated below in a more complete rejection. Applicants' arguments have been fully considered but are not deemed persuasive. Applicants argue that the prior art support enablement of expressing type I polyketide synthase genes to produce functional PKS enzymes that manufacture polyketides; Applicants cite Hutchinson as support. This argument is not found persuasive because the very limited discussion in Hutchinson is limited to type II PKS systems and in now way enables the production of functional type I PKS enzymes.

12. Previous rejection of Claims 45, 46, and 52 under 35 U.S.C. § 112, first paragraph, new matter, is withdrawn for the reasons stated above in the withdrawal of the objection to the specification.

13. Previous rejection of Claims 50 and 53 under 35 U.S.C. § 112, first paragraph, written description, related to "an int sequence" is withdrawn by virtue of Applicants' amending the claims to remove limitations to such a sequence.

14. Previous rejection of Claim 54 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of the Examiner's reconsideration in view of Applicants' arguments.

Withdrawn - Claim Rejections - 35 U.S.C. § 102

15. Previous rejection of Claims 31-37, 39, 47-49, and 55-58 under 35 U.S.C. § 102(e) as being anticipated by Khosla *et al.* (USPN 5,962,290) is withdrawn by virtue of Applicant's amendment.

Maintained - Claim Rejections - 35 U.S.C. § 102

16. Previous rejection of Claim 1 under 35 U.S.C. § 102(e) as being anticipated by Khosla *et al.* (USPN 5,962,290) is maintained. A portion of the rejection is cited below for completeness:

> "Khosla *et al.* teach a "DNA molecule which comprises a recombinant expression system for production of a hybrid modular (Type I) PKS...wherein said activities [KS, AT, ACP, etc.] are derived from at least two different modular PKS" (see Claim 10). Khosla *et al.* teach examples of genes for use in hybrid modular PKS clusters such as erythromycin, tylosin, carbomycin, spiramycin, avermectin, and candicidin (see column 14, lines 26-35). Khosla *et al.* further teach said DNA molecule operably linked to an actinorhodin (act) promoter (see Claim 17) in the presence of "actII-ORF4, an activator gene, which is required for transcription from these [actI/actIII] promoters" (see column 19, lines 38-40). Khosla *et al.* further teach host cells containing said DNAs (see Claims 11 and 18), the production of which host cells inherently require the use of vectors. Khosla *et al.* also teach methods of making modular PKSs as encoded by said DNA molecules (see Claims 12 and 19), the product of which methods is the claimed hybrid PKS enzymes of Applicants' Claim 35. Said methods of making modular PKSs are inherently also methods of making polyketides, as claimed in Applicants' Claim 39. Moreover, Khosla *et al.* teach that their methods are useful for "efficiently producing both new and known polyketides, using recombinant technology" (see column 3, lines 7-10). Lastly, Khosla *et al.* is replete with teachings of hybrid, (type I) modular PKS genes and enzymes (see for example, column 4, lines 44-65, column 9, lines 38-50, column 13, lines 53-58, and column 25, lines 24-40)."

Applicants' arguments (see paper filed November 5, 2002, Paper No. 21, pages 10-21) have been fully considered but are not deemed persuasive for the following reasons. Applicants argue the point that the genus disclosed by Khosla *et al.* does not anticipate the genus claimed in Claim 1 (among other claims rejected under 35 U.S.C. § 102(e)). The "species" limitation noted by Applicants as particular to Claim 1 and distinct from Khosla *et al.* is the combination of type I-type I hybrids. The Examiner disagrees that Khosla *et al.* do not describe type I-type I hybrids.

In USPN 5,962,290, column 10, lines 23-29, Khosla *et al.* teach "the cluster can include PKS genes derived from a single species, or may be hybrid in nature with, e.g., a gene derived

from a cluster for synthesis of a particular polyketide replaced with a **corresponding** gene from a cluster for the synthesis of another polyketide" (emphasis added). Since Khosla *et al.* do not describe genes that correspond between type I and type II PKSs, clearly the intent of the above quote is to employ type I-type I hybrids and type II-type II hybrids. Khosla *et al.* continue, "[h]ybrid clusters can include genes derived from both Type I and Type II PKSs." Thus, the first quote from Khosla *et al.* describes corresponding gene hybrids in the form of type I-type I hybrids and type II-type II hybrids and the second quote adds breath saying that type I-type II hybrids are also specifically envisioned.

Applicants also argue that Khosla *et al.* did not place the invention in the hands of the public because "Khosla '290 does not provide disclosure that enables type I/type I hybrid clusters" (emphasis in original). The Examiner disagrees. Khosla *et al.* describe type I-type I hybrids. Such hybrids are enabled to be constructed considering the state of the art of (1) known type I PKS gene clusters with defined domains, modules, and open reading frames and (2) recombinant gene technologies at the time of the invention. The Examiner relies on the state of the art of gene construction ONLY. Applicants cite this reliance as "an oblique reference to the state of the art"; however, the ability to construct a hybrid gene from two separate, known genes is well known in the art (e.g., genes encoding lacZ fusion proteins). With the description of the organization of type I PKS gene clusters and with the disclosure of specific gene cluster sequences (such as erythromycin and rapamycin) in the art, type I-type I hybrids are well-enabled considering the ability of skilled artisans to splice pieces of DNA together at the time of the invention.

Applicants further argue that type I-type I hybrid gene clusters are not enabled by Khosla *et al.* because only type II-type II hybrids are actually produced and the complex nature of the type I system does not anticipate type I-type I hybrids. With the full disclosure of the gene structures, the Examiner fails to see how the complex nature of the type I system is relevant. What is claimed is a hybrid gene, and its production is well enabled by Khosla *et al.* in combination with the skill of the art. The genes are known, domain and module boundaries are well defined, and any skilled artisan is well aware of the techniques of gene splicing. Applicants state, "simply replacing a gene encoding one activity would yield a multienzyme array that would be functional at all". However, the instant claim is drawn to a hybrid gene whose only function is to maintain an open reading frame to encode a protein. Moreover, if any further enablement is required to produce type I-type I hybrid gene clusters, the instant specification would then have to be limited in scope to those combinations it has specifically disclosed. That, however, is not the case since the understanding of the general construction of type I PKS genes alone enables type I-type I hybrid gene clusters.

Applicants further argue that type I-type I hybrid gene clusters are not enabled by Khosla *et al.* because no other type I PKS gene clusters have been sequenced. This is not the case (see MacNeil *et al.* Correlation of the Avermectin Polyketide Synthase genes to the Avermectin Structure. Annals of the NY Academy of Science (1994) 721: 123-132).

Applicants comment that the claimed invention is more than a recombinant gene product since this simplistic view would beg questions of novelty, etc. The Examiner notes that Claim 1 is drawn to a hybrid gene that is, in fact, a recombinant gene that is the combination, in reading frame, of two different genes to encode and ultimately produce a hybrid gene product.

For all of the above reasons, the instant rejection is maintained.

Maintained - Claim Rejections - 35 U.S.C. § 103

17. Previous rejection of Claim 2 under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* is maintained in the new rejection set forth below.

Applicants do not present arguments specific for the instant rejection under 35 U.S.C. § 103(a), relying on the arguments presented in the anticipatory rejections. Those arguments have been answered above for Claim 1, from which Claim 2 depends.

18. Previous rejection of Claims 25-26 and 44 under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* is maintained in the new rejections set forth below. Applicants do not present arguments specific for the instant rejection under 35 U.S.C. § 103(a), relying on the arguments presented in the anticipatory rejections. Those arguments have been answered above for Claim 1. Thus, the instant rejection is maintained.

19. Previous rejection of Claim 27 under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* in view of Kao *et al.* is maintained in the new rejections set forth below. Applicants do not present arguments specific for the instant rejection under 35 U.S.C. § 103(a), relying on the arguments presented in the anticipatory rejections. Those arguments have been answered above for Claim 1. Thus, the instant rejection is maintained.

20. Previous rejection of Claim 51 under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* in view of Cox *et al.* (USPN 5,190,871) is maintained in the new rejections set forth below. Applicants do not present arguments specific for the instant rejection under 35 U.S.C. §

103(a), relying on the arguments presented in the anticipatory rejections. Those arguments have been answered above for Claim 1. Thus, the instant rejection is maintained.

Withdrawn - Double Patenting

21. Previous warning that Claims 3 and 44 are duplicate claims is withdrawn by virtue if Applicant's cancellation of Claim 3.

22. Previous warning that Claims 36 and 47 are duplicate claims is withdrawn by virtue of the Examiner's reconsideration; the term "plasmid" has a different connotation in the art from the term "vector"; thus, both claims could be allowed since they are slightly different in scope.

Response to Arguments

23. Due to the withdrawal of several rejections in lieu of new, more complete rejections below, some of Applicants' arguments were not addressed above. Applicants' arguments are found in Paper No. 21 filed on November 25, 2002 and in Paper No. 25 filed on June 13, 2003. They will be addressed here as they pertain to newly set forth rejections in the instant Office action.

Applicants' arguments in Paper No. 21 begin with the fact that "the scope of a patent's claim is no measure of what the patent discloses" (emphasis in original). The Examiner disagrees with this statement since all patent claims must have adequate written description in the specification as originally filed to support the breadth of the claimed invention. However, the Examiner will note that a disclosed genus does not necessarily anticipate or render obvious a particular species of that genus. This issue is addressed above as it pertains to the maintenance

of the rejection of Claim 1. Moreover, as the issue related to specifying loading modules in the claims, new rejections under 35 U.S.C. § 103(a) address the issue. The Examiner notes that "identical disclosure or description" of a claimed invention need not be found in the prior art so long as the same, claimed products would have been made using the description.

Applicants' arguments in Paper No. 25 and the subsequent declarations (Paper Nos. 26 and 27) rely on the fact that Khosla *et al.* (5,962,290) does not appreciate the fact that the first AT-ACP domains constitute a loading module. Firstly, the lack of use of the term "loading module" does not diminish the ability of the prior art to anticipate or render obvious the claims pending in the instant application provided that the appropriate portions of type I PKSs would be used in hybrid gene constructs, which is clearly the case iterated in art rejections herein. Additionally, both before and after the filing of Khosla *et al.* (5,962,290) to "priming" or loading ability of the first AT-ACP was recognized (see MacNeil *et al.* and Declaration by Dr. Simpson, pages 9-10). The instant claims require no *autonomous* loading module since all the language is open claim language when referring to the first nucleic acid portion.

The Dr. Simpson declaration comments on how the "mix and match" strategy available for the small genes of a type II PKS would not have been anticipated or obvious for the larger genes of the type I PKSs (see page 13). Dr. Simpson declares, "[I]t did not occur to anyone... that the precise *in vitro* splicing together of portions of Type I PKS DNA derived from one or more natural PKS genes together with portions of an acceptor Type I PKS would give rise to a functional hybrid." Firstly, Dr. Simpson's credentials do *not* include what **all** scientists at the time of the invention where thinking. Secondly, a majority of the claims in the instant application are drawn to hybrid genes, regardless of the functional PKS that might be

functionally expressed. Thus, the ability to splice *in vitro* portions of PKS genes does enable that which Khosla *et al.* describes in USPN 5,962,290.

The Dr. Knowles declaration also notes the lack of appreciation for the loading domain by Khosla *et al.* (see page 9) and the lack of predictability of producing hybrid PKS genes (page 10). Dr. Knowles, however, does not appreciate in his declaration that only the hybrid genes themselves are claimed, not hybrid PKS genes that express hybrid PKS proteins that are correctly folded and that have adequate starter units to produce novel polyketides. The Examiner maintains that Khosla *et al.* adequately describe *in vitro* splicing of domains, modules, etc. to produce hybrid PKS genes. Moreover, the end-to-end splicing of modules does, in fact, produce functional enzymes that produce polyketides in the appropriate host cells without any further, undue experimentation, as born out by the instant application. Applicants are reminded that Khosla *et al.* is fully enabled for the scope they have described unless undue experimentation would have been necessary to go from the described, state-of-the-art, simple, *in vitro* splicing of genes to the invention claimed in the instant application.

NEW OBJECTIONS/REJECTIONS

Objections to the Specification

24. The specification is objected to for containing an embedded figure on page 89. Such figures are not permitted in the body of the specification and must be deleted and, if desired, added to the formal drawings of the application. See 37 C.F.R. § 1.58.

25. The specification is objected to for a large gap on page 94 of the specification as originally filed. From the text, it seems as though a chemical formula is missing. Applicants are advised to consider this section of the specification for any missing components. Amendment and/or comment are required.

Objections to the Claims

26. Claim 27 is objected to for having improper capitalization. The term "streptomyces avermitilis" is the proper name of a bacterium species. As such, this name must be capitalized and in italics. Correction is required.

27. Claims 44 and 68 are objected to under 37 C.F.R. § 1.75 as being a substantial duplicate of Claim 2. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See M.P.E.P. § 706.03(k). Claim 2 is drawn to a hybrid PKS gene containing a loading module and an extension module that are heterologous to each other. Claim 44, depending from Claim 67, requires the same since a loading module inherently must contain an AT domain and an ACP domain. Claim 68, depending from Claim 67, also requires a loading module and an extension module.

28. Claim 48 is objected to for having redundant language. The phrase "transformant microorganism which has been transformed" is redundant. The Examiner suggests deleting the word "transformant" in the preamble of the claim for clarity and language.

29. Claim 61 is objected to for containing a typographical error. In the fourth line of the claim, ---least--- is misspelled as "lease". Correction is required.

30. Claim 68 is objected to for containing a typographical error. In the second line of the claim, ---encodes--- is misspelled as "endoces". Correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

31. Claim 26 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "multiplicity" is unclear since it implies several but could be as few as two. In the art, numerous loading modules are specific for one of two different starter units while only the avermectin loading module is known to be "promiscuous" using several. Clarification is required.

32. Claim 54 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The "enzyme from the rapamycin system which...effects connection of the polyketide chain to an amino acid chain" is wholly unclear. On page 7 of the instant specification, this same language is used; however, the nature of the "enzyme" is wholly unclear from the specification. In the art, Aparicio *et al.* (Organization of the biosynthetic gene cluster for rapamycin in *Streptomyces hygroscopicus*: analysis of the enzymatic domains in the modular

polyketide synthase. Gene (1996) 169: 9-16) and Schwecke *et al.* (The biosynthetic gene cluster for the polyketide immunosuppressant rapamycin. Proc. Natl. Acad. Sci. (1995) 92: 7839-7843) describe the rapamycin gene cluster. It is unclear which domain "effects connection" from the art and/or the instant specification. Moreover, the location of this rapamycin segment in the hybrid PKS gene is unclear. Can it be included within the first nucleic acid portion or within the second nucleic acid portion? Such placement would not be within the scope of Claim 67 (thus, Claim 54 would not be properly further limiting as a dependent claim).

33. Claim 59 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The species *Streptomyces tsukubaensis* is unknown. The species "tsukubaensis" is known in the *Candida* genus (see attachment), but not in *Streptomyces*. Clarification and/or evidence of the species are required.

34. Claim 61 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The language of Claim 61 is confusing, particularly in citing a "**gene comprising** a plurality of **modules**" (emphasis added) since proteins have modules and genes encode proteins, but genes do not have modules. Also, the term "combinatorial module" is unclear particularly in reference to first and second points. The claim is drawn to a hybrid gene, so the use of combinatorial is unclear as to its added limitation. The overall concept of the claimed subject matter is wholly unclear for these reasons. Clarification is required.

35. Claim 62 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In view of the word "adapted" in item (a), it is unclear if the first extension module is a recombinant module (i.e., does "adapted" mean altered and non-naturally occurring as it implies). Clarification and/or amendment are required.

36. Claim 63 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In item (a), the term "the KS domain of the extension module which is homologous to said loading module" is unclear. Must this be the KS domain adjacent to the ACP of the loading module (i.e., KS1)? This limitation is implied but unclear if it is intended. Clarification and/or amendment are required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

37. Claim 52 is rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. On page 16 (last 5 lines) of the instant specification, a similar method to that

of Claim 52 is described wherein the donor DNA encodes at least an entire loading module, not just "one domain" as claimed. No support for a method using just "one domain" can be found by the Examiner. Thus, Applicants must cite clear support (page and line number) for the subject matter claimed or must delete the new matter from the application.

38. Claim 61 is rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants have cited no particular support for the claimed subject matter in their remarks. In the absence of a clear understanding of the claim (see rejection under 35 U.S.C. § 112, second paragraph above), the Examiner cannot locate support in the specification in the specification as originally filed. Thus, Applicants must cite clear support (page and line number) for the subject matter claimed or must delete the new matter from the application.

39. Claims 62 and 63 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants have cited no particular support for the claimed subject matter in their remarks. The Examiner cannot readily locate support in the specification in the specification as originally filed. Thus, Applicants must cite clear support (page and line number) for the subject matter claimed or must delete the new matter from the application.

40. Claim 67 and dependent Claims 25-27, 31-37, 39, 44, 47-51, 53-60, 64-66, and 68 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In Claim 67, the scope of "a loading module lacking a ketosynthase (KS) activity" does not have clear support in the specification as originally filed. The specification and Applicants' remarks throughout prosecution go to great lengths to discuss the inventors' identification of a "loading module" as opposed to merely naming the initial domains within the first extension module. Nowhere is a loading module described as a module "lacking ketosynthase (KS) activity". This language is particular egregious considering that post-filing date art identifies numerous loading modules that contain KS-AT-ACP domains wherein the KS is inactive by means of a Cys-to-Glu replacement in the active site of the domain (the KS^Q domain). Thus, Applicants must cite clear support (page and line number) for the scope of the subject matter claimed or must delete the new matter from the application.

41. Claim 26 is rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 26 is drawn to a hybrid PKS gene containing a loading module capable of loading any of a multiplicity of different starter units that is claimed solely by function and without any structural limitations.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, a single example of a loading module capable of loading numerous different starter units, namely the avermectin PKS loading module, is described. No description of how the structure of the avermectin loading module renders it capable of loading different starter units is found. No contrast in its structure to that of loading modules that are specific for a single starter unit is found. Thus, one of skill in the art would be unable to predict the structure of other members of this genus by virtue of the instant disclosure. Therefore, claims drawn to hybrid PKS genes containing non-specific loading modules, as a genus, are not adequately described.

42. Claim 67 and dependent Claims 25-27, 31-37, 39, 44, 47-51, 53-60, 64-66, and 68 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 67 is drawn to a hybrid PKS gene encoding a loading module lacking KS activity that is claimed solely by function and without any structural limitations.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, loading modules in the absence of KS domains are described; such modules contain acyltransferase (AT) and acyl carrier protein (ACP) domains only. However, the breadth of the claimed hybrid genes includes any loading module that lacks ketosynthase (KS) **activity**. It is evident that any loading module lacking the KS domain will also lack a KS activity; these hybrid genes are described in the instant specification. However, loading modules that lack a KS **activity** need not lack a KS domain entirely (see Witkowski *et*

al. Conversion of a β-Ketoacyl Synthase to a Malonyl Decarboxylase by Replacement of the Active-Site Cysteine with a Glutamine. Biochemistry (1999) 38: 11643-11650). In fact, in post filing date art, there are numerous examples of "inactive", KS^Q domains in the loading modules of type I PKSs. In no way does the specification as originally filed propose or describe such loading modules. Thus, while loading modules that lack a KS domain are adequately described, loading modules that lack a KS activity are not.

43. Claims 39, 57, 59, 60, 64, and 65 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods of making polyketides in microorganisms that naturally produce polyketides, does not reasonably provide enablement for methods of making polyketides in microorganisms that do not naturally produce polyketides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Claim 59 is included in the instant rejection due to its inclusion of *S. tsukubaensis*, a species of unknown origin with unknown polyketide-producing abilities. The instant claims are drawn to methods of making polyketides in microorganisms using recombinant, hybrid PKS gene expression. While all microorganisms are enabled for the expression of polyketide synthases (i.e., the enzyme can be produced), this is not the case for the subsequent production of polyketides by the polyketide synthases. To enable the full scope of the claimed methods would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as

routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In the instant specification, examples of recombinant polyketide production are limited to host cell microorganisms that naturally produce polyketides. This fact is crucial to the production of polyketides because PKS enzymes are post-translationally modified by an enzyme absent in many host microorganisms, a phosphopantetheinyl transferase (see Pfeifer *et al.* Biosynthesis of Complex Polyketides in a Metabolically Engineered Strain of *E. coli*. Science (2001) 291: 1790-1792). No guidance or examples of production of polyketides in non-polyketide host cells are described in the specification. The prior art did not address this issue at the time of the invention since only polyketide-producing host cells had been used for recombinant expression of PKSs and subsequent production of polyketides. As evidenced by post-filing date art, the requirement of posttranslational modification was wholly unpredictable at

the time of the invention. Thus, the instant claims are not enabled to the full extent of their scope.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

44. Claims 2, 25-26, 31-37, 39, 44, 47-49, 55-60, and 64-68 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,962,290) in view of MacNeil *et al.* (Correlation of the Avermectin Polyketide Synthase genes to the Avermectin Structure. Annals of the NY Academy of Science (1994) 721: 123-132). The instant claims are drawn to a hybrid PKS gene comprising a loading module from a type I PKS and an extension module from a heterologous type I PKS. The hybrid PKS gene must be operably linked to the act I promoter of *S. coelicolor* and must also be on a nucleic acid sequence containing a natural activator of act I, like actII-orf4. The instant claims are drawn to vectors, autonomously replicating plasmids, transformed *S. erythraea* and *S. coelicolor* microorganisms, and methods of making polyketides using the hybrid PKS genes. The instant claims are also drawn to the encoded, hybrid PKS enzyme.

Khosla *et al.* teach polyketide synthase (PKS) gene clusters that "can include PKS genes derived from a single species, or may be hybrid in nature with, e.g., a gene derived from a cluster for the synthesis of a particular polyketide replaced with a corresponding gene from a cluster for

the synthesis of another polyketide" (see column 10, lines 23-27). Khosla *et al.* teach examples of genes for use in hybrid modular PKS clusters such as erythromycin, tylosin, carbomycin, spiramycin, avermectin, and candicidin (see column 15, lines 13-14). Khosla *et al.* further teach PKS gene clusters operably linked to an actinorhodin (act) promoter actI/actIII in the presence of "actII-ORF4, an activator gene, which is required for transcription from these [actI/actIII] promoters" (see column 19, lines 38-42). Khosla *et al.* also teach host-vector systems using replicating phagemids(see columns 16-17) and *Streptomyces* host cells, such as *S. erythraeus* (a.k.a. *S. erythraea*) and *S. coelicolor* CH999 (see column 14, lines 1-14). Khosla *et al.* also teach methods of making polyketide using the hybrid PKS genes (see column 20, lines 45-55), which methods inherently include the production of the encoded enzyme.

Khosla *et al.* do not name the first domains of the PKS as a loading module; Khosla *et al.* consider module 1 as all of AT-ACP-KS-AT-KR-ACP (see Figure 9) (it should be noted that post filing date art describe the first AT-ACP as a loading module and the last KS-AT-KR-ACP as module 1). While Khosla *et al.* describe type I-type I hybrid PKS gene clusters wherein corresponding genes are substituted, Khosla *et al.* do not specifically describe these corresponding genes from any modular PKS other than erythromycin.

MacNeil *et al.* teach the organization of the avermectin PKS gene cluster and describe its correlation to particular domains/modules or the erythromycin PKS gene cluster (see pages 123-125 and Figure 3). MacNeil *et al.* consider the first AT and ACP domains of both the erythromycin PKS or the avermectin PKS as loading domains (see page 125, first complete paragraph).

At the time of the invention, it would have been obvious to produce the hybrid PKS gene clusters and related products because Khosla *et al.* specifically suggest such hybrids and MacNeil *et al.* provide the "corresponding genes" suggested to be combined by Khosla *et al.* It further would have been obvious to specifically combine loading modules with extension modules because loading modules "function to load the start acyl group on the PKS" (see MacNeil *et al.*) and functional PKS enzymes that, in fact, load a starter moiety are the suggested products of Khosla *et al.* One would have been motivated to combine the above teachings to produce novel polyketides via expression of hybrid PKS enzymes, wherein said novel polyketides can be therapeutically effective antibiotics (see Khosla *et al.*, Abstract and column 1). One would have had a reasonable expectation of success that hybrid type I-type I PKS genes could be effectively produced and expressed and that these hybrid PKSs, when expressed in appropriate host cells such as CH999, would produce novel polyketides due to the explicit suggestion to the fact in Khosla *et al.* and due to the extensive correlation between the avermectin and erythromycin genes described in MacNeil *et al.*

45. Claim 27 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,962,290) in view of MacNeil *et al.* and in view of Kao *et al.* (previous cited - Engineered biosynthesis of a complete macrolactone in a heterologous host. Science (1994) 265:509-512). The instant claim is drawn to nucleic acid sequences encoding hybrid modular PKS genes wherein (1) said nucleic acid sequences include at least an avr loading domain and an extender domain and (2) said loading and extender domains are heterologous.

Khosla *et al.* and MacNeil *et al.* teach as describe above. Khosla *et al.* also teach that " modular PKSs...[use] a wider range of primer units...[and] have relaxed specificity for their

starter units" (see column 25, lines 24-37). Khosla *et al.* do not teach using the avermectin loading domain in the disclosed hybrid PKS genes.

Kao *et al.* teach the relaxed specificity of the starter units of the DEBS PKS genes as well as of the avermectin PKS genes (see page 511, left column).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Khosla *et al.*, MacNeil *et al.*, and Kao *et al.* to produce the claimed invention for the reasons cited above and because the main focus of the teachings of Khosla *et al.* is the achievement of diversity in polyketide production using hybrid PKS genes and both DEBS and avermectin loading domains are known to add diversity by virtue of their relaxed starter unit specificities. One would have been motivated to produce the specific embodiment of using an avr loading domain to produce a more diversity population of polyketides for use as possible therapeutics as taught by Khosla *et al.* Moreover, one would have had a reasonable expectation of success that the claimed combination of domains would function together in view of the teachings of Khosla *et al.* and because the combination of modular PKS genes in a hybrid PKS has been shown to produce functional PKSs.

46. Claims 51 and 52 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,962,290) in view of MacNeil *et al.* and in view of Cox *et al.* (USPN 5,190,871). The instant claim is drawn to methods using nucleic acid sequences encoding hybrid modular PKS genes in host cells wherein said nucleic acid sequence are integrated into the host cell's chromosome.

Khosla *et al.* and MacNeil *et al.* teach as described above. While Khosla *et al.* teach transforming host cells with hybrid PKS genes so that said genes are retained by the host cell,

Khosla *et al.* do not teach said transformation by means of integrating into the host cell's chromosome.

Cox *et al.* teach stable integration of foreign DNA into host cell's chromosomes (see column 1, lines 25-35).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Khosla *et al.* and Cox *et al.* to practice methods of transforming using integrating plasmids because the teachings of Khosla *et al.* involve host cell transformation with antibiotic selection pressure. Gene integration is a commonly used mechanism for stable transformation. Albeit a more difficult method, said method offers more stable integration of the desired gene(s). One would have been motivated to produce the specific embodiment for more stable production of possible therapeutics as taught by Khosla *et al.* Moreover, one would have had a reasonable expectation of success that the stable integrations would function together in view of the teachings of Khosla *et al.* and because the combination of modular PKS genes in a hybrid PKS has been shown to produce functional PKSs.

Summary of Pending Rejections

47. The following is a summary of the issues pending in the instant application:

a) The drawings are considered informal.
b) The specification stands objected to for containing an embedded figure on page 89.
c) The specification stands objected to for a large gap on page 94 of the specification as originally filed.
d) Claim 27 stands objected to for having improper capitalization.
e) Claims 44 and 68 stand objected to under 37 C.F.R. § 1.75 as being a substantial duplicate of Claim 2.
f) Claim 48 stands objected to for having redundant language.
g) Claims 61 and 68 stand objected to for containing a typographical error.
h) Claim 26 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "multiplicity".

i) Claim 54 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "enzyme from the rapamycin system which...effects connection of the polyketide chain to an amino acid chain".
j) Claim 59 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the species *Streptomyces tsukubaensis*.
k) Claim 61 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for confusing language.
l) Claim 62 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in view of the word "adapted".
m) Claim 63 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "the KS domain of the extension module which is homologous to said loading module".
n) Claims 25-27, 31-37, 39, 44, and 47-68 stand rejected under 35 U.S.C. § 112, first paragraph, new matter.
o) Claim 26 stands rejected under 35 U.S.C. § 112, first paragraph, written description.
p) Claim 67 and dependent Claims 25-27, 31-37, 39, 44, 47-51, 53-60, 64-66, and 68 stand rejected under 35 U.S.C. § 112, first paragraph, written description.
q) Claims 39, 57, 59, 60, 64, and 65 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement.
r) Claim 1 stands rejected under 35 U.S.C. § 102(e) as being anticipated by Khosla *et al.* (USPN 5,962,290).
s) Claims 2, 25-26, 31-37, 39, 44, 47-49, 55-60, and 64-68 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,962,290) in view of MacNeil *et al.*
t) Claim 27 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,962,290) in view of MacNeil *et al.* and in view of Kao *et al.*
u) Claims 51 and 52 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* in view of MacNeil *et al.* and in view of Cox *et al.*

Conclusion

48. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
August 20, 2003